

REMARKS

After entry of this amendment, claims 1, 3-5, 7-33, 35-36 and 38-45 are pending. Claims 1, 31, and 33 are amended.

35 U.S.C. § 112 Rejections

Enablement

Reconsideration is respectfully requested of the rejection of claims 1, 3-5, 7-33, 35-36 and 38-45 under 35 U.S.C. § 112, first paragraph enablement requirement. Claim 1 is directed to a method for reducing the incidence of ototoxicity in a patient selected from the group consisting of a human, a cat, and a dog undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound, the method comprising administering to said patient an effective amount of an otoprotective agent comprising methionine. Claim 31 also generally requires these elements.

Claims 1 and 31 are fully enabled under 35 U.S.C. § 112, first paragraph. To expedite prosecution and without conceding the propriety of the rejection, the preventing element has been removed from claims 1 and 31. The Office also asserts that claims 1, 31, and the claims that depend therefrom are not enabled with respect to undergoing treatment with other platinum-coordinating compounds.¹ In this connection, the Office notes that applicant must provide a disclosure of how to make and use the full scope of the claimed invention without undue experimentation."²

But the Office cannot make a proper rejection by merely quoting general principles of law. As acknowledged in M.P.E.P. § 2164.04, the court in *In re Marzocchi* held that:

"it is incumbent on the Patent Office whenever a rejection [for enablement] is made, to explain *why* it doubts the truth or accuracy of any statement in the supporting disclosure and to back up such assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement."³

The Examiner appears to be relying solely upon the breadth of the claims as a basis for doubting enablement. A rejection for merely for breadth, however, is not appropriate, as explained in *In*

¹ Page 3 of the Office action dated September 10, 2007.

² *Id.*

³ *In re Marzocchi*, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1971).

Re Borkowski,⁴ *In re Robins*,⁵ and in *Marzocchi* itself. Here, the specification provides information regarding the anti-tumor platinum-coordination compounds and the effectiveness of methionine for reducing the incidence of ototoxicity arising from their administration. This information would have provided guidance for the administration of anti-tumor platinum-coordination compounds other than cisplatin and satisfy the "how to make and use" requirement.

Moreover, in response to the Office's recitation of the Wands factors, Applicant asserts that claims 1, 31, and the claims that depend therefrom are enabled under this standard. With respect to the predictability in the art factor, the claims are directed to the application of only a single compound, i.e., methionine and salts thereof in any combination of the various asymmetric isomers. Certainly it cannot be undue experimentation to confirm the efficacy of these few isomers and isomer mixtures of a single compound against the various antitumor platinum-coordination compounds using known methods of evaluation.

Applicant's respectfully suggest that the Examiner has confused different enablement issues in asserting that:

whether methionine will bind to other platinum-coordinating compounds and protect against ototoxicity is not known or predictable based on Applicant's disclosure.

and then attempting to support the point by quoting Applicant's statement at p. 8, lines 19-23 that 'The foregoing discussion demonstrates that it is not possible to predict reliably which particular sulfur-containing nucleophile will exhibit a platinum-containing compound protective effect in any particular cell tissue, or organ.'⁶

This mixes apples and oranges. The unpredictability suggested by Applicant supports the non-obviousness under §103 of the selecting methionine among an essentially unlimited class of "sulfur containing nucleophiles." It has no bearing on the extent of experimentation required to support the enablement of the invention with respect to a much more limited class of antitumor platinum-coordination compounds.

Additionally, the amount of direction or guidance provided is in favor of finding enablement. Applicant states that methionine is effective as an otoprotectant for antitumor

⁴ 164 U.S.P.Q. 642 (C.C.P.A. 1970).

⁵ 166 U.S.P.Q. 552 (C.C.P.A. 1970).

⁶ Page 6 of Office action dated September 10, 2007.

platinum-coordinating compounds and except for objecting to the breadth of the genus, the Office has not provided cogent reasoning to doubt Applicant's specification.

Further, the Office has failed to provide evidence why one of ordinary skill in the art would have considered that a large number of the anti-tumor platinum-coordination compounds disclosed would either not produce ototoxicity, or if such ototoxicity was produced, why methionine administration would not reduce the incidence of ototoxicity. Furthermore, and in any event, the experimentation required to test for methionine's protectant effect against each anti-tumor platinum-coordination compound's ototoxicity is not undue because a person of ordinary skill would know how to test methionine against each compound and such testing would be routine. Thus, claims 1, 31, and the claims that depend therefrom satisfy the enablement requirement of 35 U.S.C. § 112.

Claim 33 is directed to a method for reducing the incidence of ototoxicity in a patient undergoing treatment with an aminoglycoside antibiotic, the method comprising administering to said patient an effective amount of an otoprotective agent comprising methionine. Similar to the reasons cited above for claims 1 and 31, the Office has failed to provide evidence why one of ordinary skill in the art would have considered that a large number of the aminoglycoside antibiotics disclosed would either not produce ototoxicity, or if such ototoxicity was produced, why methionine administration would not reduce the incidence of such ototoxicity. Furthermore, and in any event, the experimentation required to test for methionine's protectant effect against each aminoglycoside antibiotic's ototoxicity is not undue because a person of ordinary skill would know how to test methionine against each compound and such testing would be routine. Thus, claim 33, and the claims that depend therefrom satisfy the enablement requirement of 35 U.S.C. § 112.

Further, the Examiner asserts that "'preventing' is an absolute term meaning that a patient will never develop ototoxicity, of any degree..."³ Although to expedite prosecution, the term preventing has been removed from claims 1, 31, and 33, a medical dictionary defines preventive as "to come before, prevent" and lists prophylactic as a synonym.⁴ Accordingly, the term "prevent" is construed using the plain meaning of the term to mean that the agent is administered prior to the event, as it comes before or is a prophylactic. Additionally, "prevent" does not have

³Page 5 of the Office action dated September 10, 2007.

⁴Stedman's Medical Dictionary, 26th Edition, 1995.

the same meaning as the term “cure,” because in the medical context, cure implies that the agent is administered after the patient has been in a diseased state, since it is defined as a “restoration to health.”⁵ Therefore, prevention is not synonymous with cure and a method for preventing ototoxicity as construed above means that the anti-ototoxic agent is administered prior to the event and it does not require a method for treatment with absolute success.

The claims at issue recite methods of “reducing the incidence of ototoxicity.” When read in the context of the claims and specification as a whole, the incidence of ototoxicity is reduced by administering the otoprotective agent of the invention to a subject in need thereof; this administration could be prior to, simultaneous with or subsequent to the onset of ototoxicity.

Moreover, reducing the incidence of ototoxicity includes preventing ototoxicity. To reduce the incidence of ototoxicity, the care can be prophylactic. In addition, the care can be simultaneous with or after the onset of the ototoxicity. Thus, to reduce the incidence of ototoxicity, the agents are administered prior to, simultaneous with or after the onset of the ototoxicity; whereas, as detailed above, to prevent ototoxicity, the compositions are administered prior to the onset of the ototoxicity. Neither term requires a “cure.”

Written Description

Reconsideration is respectfully requested of the rejection of claims 1, 3-5, 7-14, 18-33, 35-36, and 38-45 under the 35 U.S.C. § 112, first paragraph written description requirement. Claims 1 and 31 are described above in connection with the enablement rejections. Applicant fully possessed the invention described by claim 1 and 31 at the time of filing and the specification conveys this to one skilled in the art. The Office cites *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 U.S.P.Q. 2d 1398 (Fed. Cir. 1997) for the proposition that “structure, formula, chemical name, or physical properties are needed to satisfy the written description requirement.”⁷ The Office’s reliance on *Eli Lilly* in this situation is misplaced. As the Office admits, the *Eli Lilly* case was decided within the factual context of DNA sequences.⁸ For example, in *Eli Lilly*, the cDNA sequence for human insulin had not been characterized. However, as held by the Court of Appeals for the Federal Circuit in *Capon v. Eshhar*, when

⁵See id.

⁷ Page 10 of Office action dated September 10, 2007.

⁸ Page 10 of Office action dated September 10, 2007.

DNA sequences are known in the art, it is not necessary to determine the sequence afresh to satisfy the written description requirement.⁹ As distinguished from the uncharacterized cDNA of *Eli Lilly*, the anti-tumor platinum-coordination compounds described in the specification have been used as chemotherapeutic agents for more than 30 years and a person of skill in the art would have been very familiar with the genus having this description. Moreover, these anti-tumor platinum-coordination compounds are described in the specification as water-soluble and a representative number of compound names are provided on page 33. Therefore, since the anti-tumor platinum-coordination compounds are a well-known class of compounds, applicant need not set out the information already known in the art. In sum, claims 1, 31, and the claims that depend therefrom satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.¹⁰

For reasons similar to those outlined above with regard to claims 1 and 31, the specification unquestionably conveys to one skilled in the art that the Applicant fully possessed the invention described by claim 33 at the time the application was filed. Claim 33 requires reducing the incidence of ototoxicity in a patient undergoing treatment with an aminoglycoside antibiotic. These aminoglycoside antibiotics are described in the specification on page 34 as containing one or more sugar moieties and a streptidine ring, and having one or more amino or guanidino groups. Further, a representative number of aminoglycoside antibiotics is listed in the specification. Thus, claim 33, and the claims that depend therefrom satisfy the written description requirement of 35 U.S.C. § 112, first paragraph.

35 U.S.C. § 103 Rejection

Reconsideration is respectfully requested of the rejection of claims 1, 3-5, 8, 10-17, and 19-32 as being unpatentable over Basinger et al. (*Toxicology and Applied Pharmacology*, 1990, vol. 108, pages 1-15).

⁹ Capon v. Eshhar, 418 F.3d 1349 (Fed. Cir. 2005).

¹⁰ Applicant respectfully submits that the exceptional issues in *Eli Lilly* are entirely unrelated to the more conventional written description issues in this case. The University of California claims were "single means" claims based exclusively on function with no requirement of structure or articulation of physical or chemical properties associated with structure. Here the claims are definitively directed to methionine and a recognized class of antitumor platinum-coordination compounds, the structures of which are well known.

Claims 1 and 31

Claim 1 is described in more detail above. Thus, the issue is whether it would have been obvious to treat cisplatin-induced ototoxicity by administration of methionine. Inherency (or whether an effect will naturally result) has no relevance to obviousness of a method claim that is directed to treatment of another condition unrecognized in the prior art. As the C.C.P.A has stated in reversing an obviousness rejection of a claim to a method of treating a specified condition with a defined treatment agent based on the inherent effect of treating a different condition with a similar agent.

[Inherency] is quite immaterial if, as the record establishes here, one of ordinary skill in the art would not appreciate or recognize that inherent result, *in re Shetty*.¹¹

The method claims at issue in *Shetty* were directed to methods for appetite control and the cited prior art disclosed compounds and dosages useful for combating microbial infestation. The *Shetty* court stated that the Office had "failed to show a reasonable expectation, or some predictability" that the prior art compound disclosed in the first reference would be an effective appetite suppressant if administered in the dosage disclosed in the second reference and that the Office's hindsight assertion that the dosages would make the weight loss method obvious was insufficient.¹² Similar to *Shetty*, claims 1 and 31 recite a method for reducing the incidence of ototoxicity while the reference cited against these claims disclose methods for reducing the incidence of nephrotoxicity. Thus, claims 1 and 31 are patentable over the cited references.

Further, the court in *Ex parte Zbornik* found a process for treating Air Sac Infection in fowl patentable over prior art disclosing substantially the same compound to treat ducks for malaria.¹³ The *Zbornik* court found that the claims were patentable because the cited reference was not concerned with appellant's problem and it failed to suggest its solution. Similarly, the cited reference is concerned with reducing nephrotoxicity, not ototoxicity, and it fails to suggest to a skilled person that methionine would provide otoprotection to a patient undergoing treatment with a chemotherapeutic effective amount of an anti-tumor platinum-coordination compound.

Basinger et al. merely disclose that administration of L-methionine with cisplatin reduces the nephrotoxicity known to arise from cisplatin administration. The reference does not disclose

¹¹ 195 U.S.P.Q. 753.

¹² See id. at 756.

¹³ *Ex parte Zbornik*, 109 U.S.P.Q. 508.

nor suggest that L-methionine or any other composition would inevitably be effective to protect against ototoxicity. The text of Basinger only mentions ototoxicity as a possible side effect of cisplatin administration. To the extent it has any relevance at all, the reference would have led a person of ordinary skill to believe that L-methionine was only effective as a nephroprotectant.

Furthermore, there is much evidence that different causes of ototoxicity have different mechanisms and as such a specific nephroprotectant such as L-methionine may or may not be effective for ototoxicity. This knowledge of the differences in mechanisms for different causes would not have led one of ordinary skill from the use of L-methionine as a nephroprotectant for cisplatin administration to the use of methionine as an otoprotectant for cisplatin administration.

Moreover, even with the benefit of hindsight, administration of an inherently ototoxic dosage of cisplatin cannot be demonstrated in any method suggested by the cited reference. Even in the context of novelty under §102, inherency may not be established if there is only a probability or possibility that a certain result may occur.¹⁴ Certainly, no less a standard can apply with respect obviousness under §103 where the actual teachings of the references are relatively more remote than in the case of novelty. In the present case, administration of cisplatin in accordance with the combined disclosures would not have necessarily and inevitably resulted in the occurrence of ototoxicity in a subject. As explained above, Basinger et al. describe the effects of L-methionine on nephrotoxicity. There is no disclosure that the doses of cisplatin administered would provide more than a mere possibility that some of those subjects might also suffer from ototoxicity. Basinger et al. state that nephrotoxicity was considered to be the dose-limiting toxicity for cisplatin administration.¹⁵ Thus, patients typically suffered nephrotoxic effects of cisplatin at lower doses than other toxicities.

Additionally, in 1995, the human doses of cisplatin included 20 mg/m² I.V. daily for 5 days every three weeks and single dose of 50-100 mg/m² every 4 weeks.¹⁶ It was further reported that nephrotoxicity was the "major dose-limiting toxicity of Platinol" (Platinol is an aqueous solution of cisplatin).¹⁷ Additionally, it was reported that nephrotoxicity occurred in about 28-36% of patients given a single dose of 50 mg/m² cisplatin and ototoxicity occurred in

¹⁴ *In re Oelrich*, 666 F.2d 578.

¹⁵ See page 2.

¹⁶ Platinol-AQ Data Sheet, January 1995.

¹⁷ See id.

up to about 31% of patients given the same 50 mg/m² cisplatin dose.¹⁸ In other studies, fewer patients experienced ototoxicity (e.g., clinical hearing loss) than nephrotoxicity.¹⁹ In these reports, the majority (69% in one report) did not experience ototoxicity. Thus, there is not more than a mere possibility that ototoxicity will occur for many therapeutic doses of cisplatin and ototoxicity certainly does not inevitably or necessarily result upon the administration of cisplatin in the range of doses disclosed in the cited references. Therefore, claims 1, 31, and the claims that depend therefrom satisfy the requirements of 35 U.S.C. § 103(a).

¹⁸ See id.

¹⁹ Planting et al., *Cancer Chemotherapy and Pharmacology* 1997, 40(4), 347-352.

CONCLUSION

Applicant submits that the present application is now in a condition for allowance and requests early allowance of the pending claims.

The Commissioner is hereby authorized to charge any under payment or credit any over payment to Deposit Account No. 19-1345.

Respectfully submitted,



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